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William W. Thoms, Jr., MD, Guest Editor

Giulio J. D'Angio, MD, Series Editor, and Audrey E. Evans, MD, Associate Editor

Multimodal Management of Recurrent Wilms' Tumor: The Role of Radiation Therapy

William W. Thoms, Jr., MD, Roger Vega, MD, Carlos Abramowsky, MD, Richard Ricketts, MD, and Brad Wyly, MD

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William W. Thoms, Jr., MD (Radiation Oncologist)

The patient to be discussed gives us the opportunity to explore multimodal retrieval strategies in pediatric oncology. Focus will be placed on the role of radiation therapy (RT) in salvage attempts. This is because RT is sometimes excluded as being too damaging. There are techniques available to reduce normal tissue injury, as this Tumor Board will make clear.

S.S. is a 5-year-old black female diagnosed with Wilms' tumor in May, 1993 when she presented with a left flank mass. Preoperative computed axial tomography scan of the chest, abdomen, and pelvis showed a 15 cm inhomogeneous mass arising from the upper pole of the left kidney. No distant metastatic disease was noted. On May 28, 1993 she underwent a left nephrectomy, exploratory laparotomy, and retroperitoneal node sampling. Intraoperative findings included a left renal mass adherent to the diaphragm. A portion of the diaphragm was removed with the nephrectomy specimen. No tumor spillage was noted. The contralateral kidney was normal. Her postoperative course was unremarkable. Pathologic review showed favorable histology Wilms' tumor. Margins of resection were negative. Tumor invaded, but did not completely penetrate, the renal capsule. An inflammatory pseudocapsule was present at the site of adherence to the diaphragm. All lymph nodes were free of tumor. She was enrolled on the National Wilms' Tumor Study 4 on the Stage I arm. She initiated chemotherapy on June 3, 1993 according to regimen EE4A, being treated with vincristine 1.5 mg/m^2/week for ten doses and dactinomycin 45 mcg/kg/d, delivered on Day 0 of weeks 0, 3, and 6. On August 24, 1993 and September 14, 1993 she received vincristine 2.0 mg/m^2 and dactinomycin, 45 mcg/kg. Her last dose of vincristine was on October 19, 1993. Upon restaging on November 16, 1993 she underwent an abdominal ultrasound which showed a mass in the soft tissues of the left posterior abdominal wall. Laparotomy on December 13, 1993 revealed a tumor mass arising from the left upper posterior abdominal wall which was completely excised.

Dr. Wyly, what were the radiographic features of the recurrent nodule?

Brad Wyly, MD (Diagnostic Radiologist)

The initial CT scan of the abdomen showed a 15 cm inhomogeneous enhancing mass arising from the upper pole of the left kidney, filling the left abdomen, and displacing the spleen anteriorly, superiorly, and medially (Fig. 1). There was normal enhancement of the inferior vena cava without tumor thrombus. No focal mass of the right kidney was seen. No metastases were noted. A color Doppler ultrasound of the abdomen on May 27, 1993 with a 5 mHz sector probe confirmed the above findings.

The recurrent nodule was first identified in the left posterior abdominal wall on ultrasound. It showed an

From the Departments of Radiation Oncology (W.W.T.), Pediatrics (R.V.), Pathology (C.A.), Surgery (R.R.), and Radiology (B.W.), Emory University School of Medicine, Atlanta, Georgia.

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Address reprint requests to Giulio J. D'Angio, M.D., Department of Radiation Oncology, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104, and other correspondence to William W. Thoms, Jr., M.D., Department of Radiation Oncology, Emory University School of Medicine, 1365 Clifton Rd., Atlanta, GA 30322.

Fig. 1. Contrast enhanced CT scan of the abdomen showing the primary left renal Wilms' tumor (arrows) displacing the spleen (S).

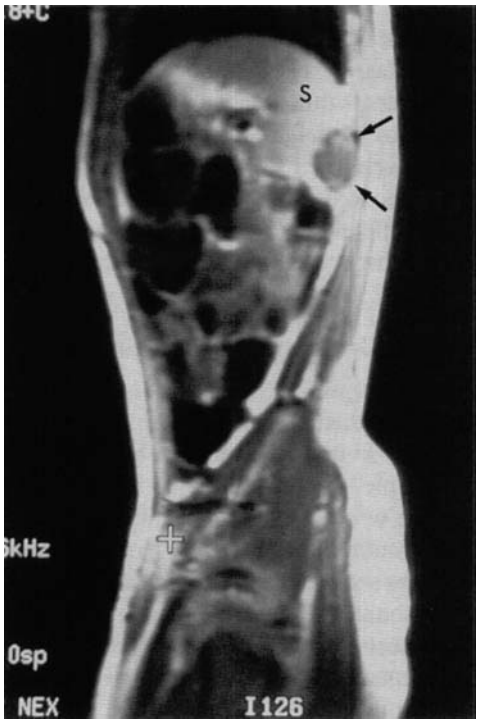

Fig. 2. Parasagittal magnetic resonance image of the recurrent tumor nodule (arrows) adjacent to the spleen (S).

echogenic mass lateral to the lower aspect of the spleen and measured 3.2 × 2.7 × 1.8 cm. An MRI with gadolinium showed an enhancing hyperintense mass between the lower spleen and the posteroinferior chest wall. No mass in the right kidney or liver was seen (Fig. 2).

Other radiologic studies, including chest CT, failed to identify any other sites of metastatic disease.

Dr. Thoms. Dr. Ricketts, did your surgical findings confirm the diagnostic imaging findings?

Richard Ricketts, MD (Pediatric Surgeon)

At the time of resection, we found the nodule to be located in the upper posterior abdominal wall, cephalad to the insertion of the diaphragm. It was not visible until the diaphragm was opened and so was at least partly within the thoracic wall. It was, however, extrapleural, and without pulmonary involvement. The nodule was not in continuity with the renal tumor bed, and in gross appearance was more consistent with a ganglioneuroma than Wilms' tumor. It was excised completely and without difficulty. Thorough examination of the abdomen and chest failed to identify any other sites of recurrent tumor.

Dr. Thoms. Dr. Abramowsky will now review the pathologic findings.

Carlos Abramowsky, MD (Pathologist)

The findings from this patient's nephrectomy specimen were consistent with favorable histology Wilms' tumor. The outer convexity of the tumor had an inflammatory pseudocapsule. The renal capsule was felt to be invaded but not completely penetrated, although the presence of a pseudocapsule and newly formed reactive layers of tissue around the tumor often confound one's ability to identify extension beyond the kidney. It is therefore possible that this nodule represents a lymphatic metastasis from a site of diaphragmatic invasion. The remainder of the pathologic material from this operation were consistent with a Stage I tumor. The initial pathology was reviewed with Dr. Bruce Beckwith, who concurred with the findings.

The recurrent nodule consisted of 90% necrotic tumor. In one fragment, after extensive sampling, a microscopic focus of well-preserved tumor tissue was noted (Fig. 3). This periphery of the tumor nodule showed a well-established granulation tissue and fibroblastic response, suggesting that the nodule had been there for weeks only as opposed to months. I cannot be certain if the necrosis was due to chemotherapy response, lack of a vascular supply or both. The nodule was excised with negative margins.

Dr. Thoms. What systemic salvage options are available for this patient?

Roger Vega, MD (Pediatric Oncologist)

The survival of relapsed Wilms' tumor patients is approximately 30% at 3 years. Although original Stage I, favorable histology patients with recurrent tumor have been reported to have survival rates as high as 57% at 3 years, patients who relapse within 5 months of nephrectomy seem to have a poorer prognosis [1–3]. Because of the initial favorable histology and solitary location of relapse, the choice of systemic agents for treatment in this case include doxorubicin, vincristine, and dactinomycin.

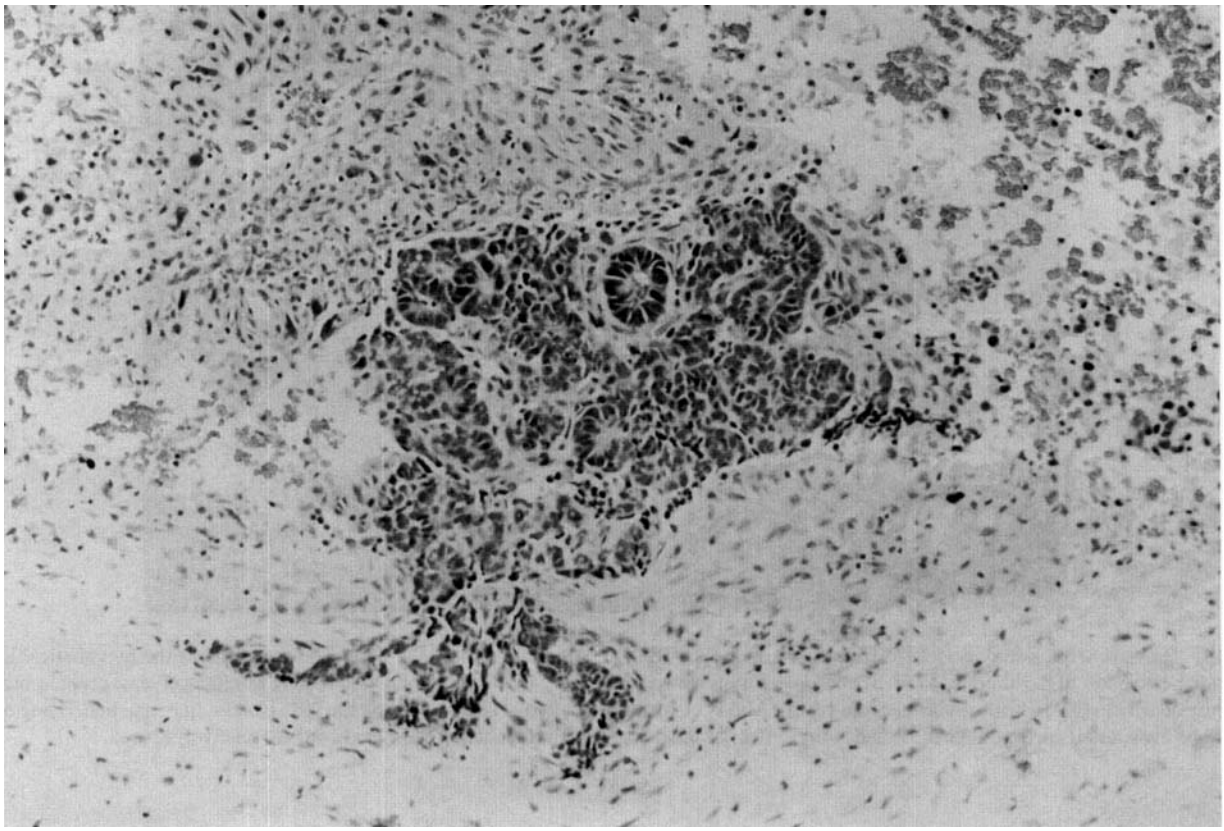

Fig. 3. Enlarged photomicrograph of the recurrent tumor nodule showing the microfocus of residual Wilms' tumor surrounded by necrotic tissue.

Doxorubicin is a cornerstone of this child's salvage regimen. It has demonstrated activity as a retrieval drug and is used in the therapy of unfavorable primary tumors [2]. The use of vincristine and dactinomycin is less clear in this situation, but responses to retreatment with these drugs in relapse have been reported. The demonstration of early failure implies that the tumor may be resistant to these agents, although the 10-week duration of therapy may not have been sufficient in this case. We intensified the regimen by prolonging the course of salvage treatment to 54 weeks. Alternative agents such as ifosfamide, cyclophosphamide, and cisplatin have not demonstrated significantly higher response rates in this setting [2–5]. The toxicity of these agents is higher, especially in the case of cisplatin. Does radiotherapy fit into the salvage regimen? If so, when should it be administered?

Dr. Thoms. Radiotherapy is an important contributor to the salvage treatment regimen for several reasons. It is a component of the primary treatment protocols for advanced and unfavorable Wilms' tumor because of its activity in this disease. It has been favorably associated with treatment of relapsed Wilms' tumor patients [2]. Lastly the focal nature of the relapse makes the use of a local treatment modality very appropriate.

The initial treatment volume in this case should be to the left flank to include both the primary tumor bed and the site of the recurrent tumor with at least a 2 cm margin. This volume would be treated to 10.8 Gy in 1.8 Gy fractions using anterior and posterior fields. A boost to the site of the recurrent tumor in the posterior abdominal and thoracic walls using the electron beam would then be given to a total dose of 21.6 Gy in 1.8 Gy fractions. This treatment plan addresses the risk of additional subclinical residual tumor in the primary tumor bed as well as the increased risk of microscopic disease in the recurrent tumor site (Fig. 4).

Timing of radiotherapy is important. The use of irradiation within the first 2 weeks after surgery is a basic component of primary treatment of Wilms' tumor. It seems logical to follow a similar plan in this case.

Dr. Vega. With respect to the use of both irradiation and doxorubicin in this patient, should any precautions be taken regarding subsequent doses of this drug?

Dr. Thoms. Reductions in subsequent doses of Adriamycin; that is, doxorubicin, are reserved for patients receiving either whole lung irradiation or whole abdominal irradiation in the primary treatment of Wilms' tumor. The reduction is advocated because of the increased prob-

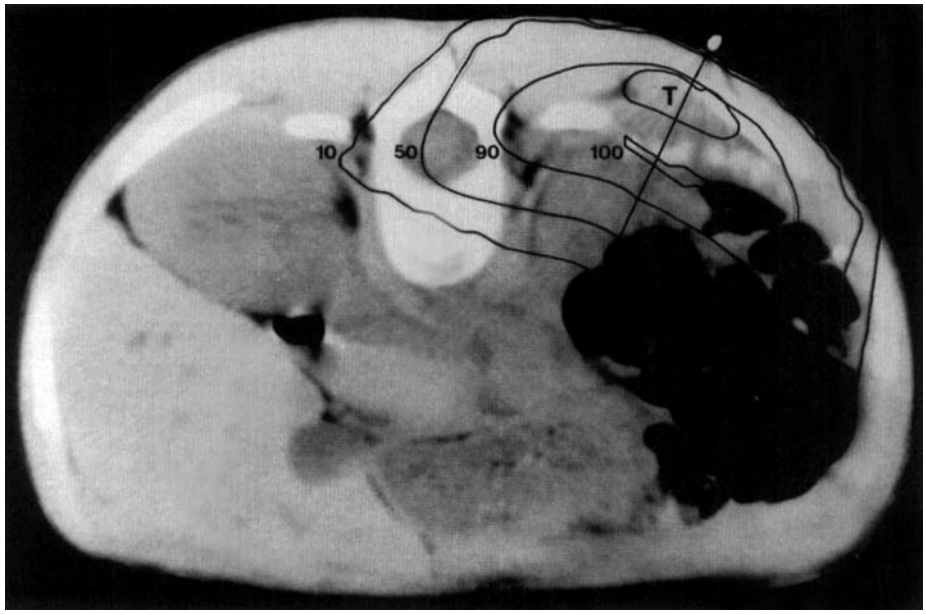

Fig. 4. Treatment plan and isodose distributions of the 12 MeV electron beam boost to the tumor bed (T). The isodose curves are based on unity density tissues. The doses beneath the vertebral body elements would be even less if corrected for the "shadowing" effect of the bony structures. Thus, the doses shown represent the hypothetical highest dose the electron-irradiated tissues would receive. As represented, the tumor is encompassed by the 90% isodose line, and underlying normal tissues including the spinal cord are relatively spared.

ability of interaction of these agents with radiation therapy leading to significant, and, at times, fatal complications [6,7]. The relatively large volume of irradiated lung and heart, calls for a reduction in the doxorubicin dose in the first postirradiation cycle in this case. Customized metal shielding will be used to exclude as much cardiac tissue as possible from the irradiated volume. The use of the electron beam allows treatment of the tumor bed with substantially less dose to the heart when compared to photon irradiation. This is because of the characteristically steep dose reduction gradient after the electron beam exits the irradiated volume at risk for residual tumor. Normal tissues outside the tumor bed can therefore be preferentially spared radiation exposure.

Dr. Ricketts. Will the use of radiation in this situation lead to any significant complications such as scoliosis or second malignancy?

Dr. Thoms. The incidence of musculoskeletal deformity in advanced stage children receiving radiation and chemotherapy, usually including doxorubicin, may be as high as 50% [6]. The frequency of second malignant neoplasia is approximately 1% at 10 years after diagnosis, may be expected to continue to increase with time, but remains under 5% at 20 years [8]. An additional concern is the incidence of cardiac abnormalities being identified in long term survivors. This would be particularly relevant in this child who has a left sided recurrence and is being treated with both doxorubicin and radiotherapy [6].

GUEST EDITOR'S NOTE

The evolution in the management of Wilms' tumor represents one of the triumphs of multimodality cancer care, but a systematic approach to the therapy of relapsed patients has not been developed. To some extent, this is due to the small number of recurrences, and to differences in the initial treatment regimens which are based on histologic type and stage. These differences preclude the development of a uniform approach to salvage therapy. The development of new agents with demonstrable activity in Wilms' tumor should be pursued vigorously. Nevertheless, a relatively high percentage of relapsed patients can be salvaged using existing agents in more intensive fashion. A higher cost in terms of late effects may be the inevitable price; but those secondary to irradiation can be kept within bounds through appropriate treatment planning. In our patient, electron beam therapy enabled us to treat the region at highest risk for recurrence up to full dose while sparing underlying sensitive structures.

As of May 1995 this patient remains free of disease. No pulmonary or cardiac toxicity has been noted.

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SERIES EDITOR'S NOTE[1]

Nineteen hundred and ninety-five marks the 100th anniversary of the epochal discovery of the X ray by Wilhelm Conrad Röntgen (1845–1923). Educated in Holland, where he was not an outstanding student, his education continued first at the University of Utrecht, and then the famous Federal Institute of Technology in Zurich. There, his interest in science was furthered by outstanding teachers. He advanced academically, and held intermediate posts before being appointed Professor of Physics and Director of the Institute of Physics at the University of Würzburg in Germany. Physics experimentation after energizing bipolar vacuum tubes of various designs, such as the ones by W. Hittorf and by W. Crookes, was very active in many centers at that time. While not designed for that purpose, these "cathode ray" tubes proved to be a source of X rays.

Röntgen preferred to work after hours, and was conducting experiments late one November night in a faintly illuminated laboratory. He saw luminescence in some barium platinocyanide crystals that lay nearby when the tube was energized. Crookes himself had identified darkening of glass photographic plates, but—unlike Röntgen—had failed to ask the all-important question, "Why?" Röntgen not only asked the question but also found the answer in a brilliant series of experiments. In a few short weeks, he had accurately identified the nature of these rays, which did not fit any others that were known to physicists at that time; hence, the term "X rays". His subsequent report is a model of simplicity and direct writing [2]. It starts:

> "1. If one passes the discharges of a fairly large . . . induction coil through a Hittorf vacuum tube. . ., one observes in the completely darkened room that . . . barium platinocyanide . . . glows brightly or becomes fluorescent with each discharge. . . ."

He received the richly-deserved Nobel prize in physics in 1901 for his discovery. It is of interest that he objected to having his name associated with the X ray, because he thought, "Röntgen ray" debased his family name [1].

His observation was serendipitous,[2] as so many major discoveries in science have been. The difference between a seminal observation and a shrug of the shoulders is well-exemplified by the discovery of the X ray as we already have seen. Similarly, it is little known that the first X-ray picture was actually obtained at the University of Pennylvania (UP) [1,3]. On November 22, 1890, almost exactly 5 years before Röntgen's discovery, UP physicist Arthur W. Goodspeed was conducting experiments in the presence of a guest, N. Jennings. The latter was a photographer interested in the photographic images produced by the spark caused by the relatively high voltages used in Crookes' tubes. Jennings was using coins for his trolley fare to produce the photographic images. He placed some of them in the meantime on unexposed photographic plates, which were enclosed in dark wrappings to protect them from light. These supposedly unexposed plates were later developed by Jennings who reported that one of them showed two circular shadows that he could not explain. He reported the matter to Goodspeed, who, in essence, shrugged his shoulders and put the plates aside until Röntgen's 1895 report struck a responsive cord. Goodspeed promptly reproduced the Jennings images using the 1890 experimental set-up and published the original image obtained by him and Jennings in a report dated 1896 [4]. In so doing, he was careful to state that neither he nor Jennings claimed any credit for the image, which was accidental. He wished only to record the image for the sake of history. Glasser quotes Goodspeed as having said during a lecture on February 22, 1896, "We can claim no merit for the discovery, for no discovery was made. All we ask is that you remember . . . that . . . the first picture in the world by cathodic rays was taken in the physical [sic] laboratory of the University of Pennsylvania" [1].

The ferment in research that resulted from Röntgen's publication is not difficult to imagine, but the productivity remains amazing. Within weeks, the biological effects

[1]Biographical data from Reference 1 and from Firkin BG, Whitworth JA: "Dictionary of Medical Eponyms." Park Ridge, NJ: Parthenon Publishing Group Inc, 1989.

[2]This term was apparently coined by Horace Walpole in 1754, deriving it from a Persian fairy tale concerning the three Princes of Serendip (from Arabic: *Sarandap*), this being the ancient name of Ceylon, now Sri Lanka. The three princes, travelling for other reasons, kept making unexpected but happy discoveries along the way; hence, "serendipity."

were first appreciated through serendipitous clinical observations. It became obvious from the radiation burns suffered by the early workers that Röntgen rays produced damage in normal skin cells. Extension of this reasoning led within 6 weeks to treatment of the first patient: a woman with carcinoma of the breast, irradiated by E.H. Grubbé in Chicago in January of 1896 [5,6]!

The first planned radiobiologic experiments were perhaps those of G. Perthes in 1903 [7]. He reported the effects of irradiating one wing of a chick, noting it did not grow normally as compared to the unirradiated limb on the opposite side. The conclusions regarding children were obvious, and have influenced pediatric oncologists ever since. Thus, in less than 10 years after Röntgen's discovery, the hazards and potential benefits of pediatric radiotherapy had already become established. This Proceedings reflects this understanding, and demonstrates one method used by pediatric radiation therapists to gain the benefits while minimizing the adversities.

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